UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,680	01/10/2000	HANS-PETER SCHWARZ	BHV-313.01	6277

7590 01/14/2004

Baxter Healthcare Corp
P O Box 15210
Irvine, CA 92623-5210

EXAMINER	
FLOOD, MICHELE C	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,680	SCHWARZ ET AL.	
	Examiner	Art Unit	
	Michele C. Flood	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-49,51-62,73 and 75-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *43-49,51-62,73 and 75-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continued Prosecution Application

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of 47-49 are rendered uncertain because the percentage amounts of the ingredient are not set forth in terms of either "by weight" or "by volume" percentage amount. The lack of clarity renders the claims indefinite since the resulting claims do not clearly set forth the metes and bounds of the patent protection desired.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 43-49, 51, 52, 55-57, 62, 73, 75-79, as amended, and newly submitted Claims 82-84 remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Chandra et al. (A). The rejection stands for the reasons set forth in the previous Office action and for the reasons set forth below.

Applicant claims a method of inactivating microorganisms and pyrogens present in a biological material comprising: adsorbing a biological material to a solid carrier, wherein the biological material comprises proteins; and incubating the biological material in the presence or an alkyl phosphate-free detergent solution, wherein the detergent solution contains at least one eluotropic salt in a total concentration of at least 200mM, wherein during incubation the proteins are desorbed into the detergent solution to yield a suspension and the microorganisms and pyrogens are inactivated. Applicant further claims the method according to claim 43, wherein the microorganisms are viruses; wherein the elutropic salt is an alkaline earth salt; wherein the elutropic salt is sodium chloride; wherein the detergent is in an amount of at least 1%; wherein the detergent is in an amount of at least 5%; wherein the detergent is in an amount of at least 10%; and, wherein the detergent is selected from the group consisting of polysorbates and polyoxyethylene ethers. Applicant further claims the method according to claim 51, wherein the polyoxyethylene ether detergent is non-ionic. Applicant further claims the method according to claim 43, wherein the incubating is performed for a period ranging from about 10 minutes to 10 hours; wherein the incubating is performed for a period ranging from about 1 hour to 5 hours; and, wherein the biological material is selected from the group consisting of plasma, a plasma fraction, a blood factor, a vitamin K-dependent protein, a prothrombin complex-containing fraction and a material from a cell culture. Applicant claims a method of inactivating microorganisms and pyrogens present in biological materials, wherein the method comprises: adsorbing a biological material to a solid carrier, wherein the

material comprises proteins; incubating the biological material in the presence of an alkyl phosphate-free detergent solution, wherein the detergent solution contains at least one eluotrophic salt in a total concentration of at least 200mM, wherein during incubating the proteins are desorbed into the detergent solution to yield a suspension and the microorganisms and pyrogens are inactivated: and purifying proteins from said suspension to yield a biological preparation. Applicant further claims a suspension prepared according to claim 43. Applicant further claims a suspension prepared according to claim 62. Applicant claims a biological preparation obtainable by a method of inactivating microorganisms and pyrogens in a biological material, wherein the method comprises: adsorbing the biological material in the presence of an alkyl phosphate-free detergent solution, wherein the detergent solution contains at least one eluotropic salt in a total concentration of at least 200mM, wherein during incubating the proteins are desorbed into the detergent solution to yield a suspension and the microorganisms and pyrogens are inactivated; and purifying said proteins from the suspension to yield the biological preparation. Applicant further claims the biological preparation according to claim 76, wherein the preparation comprises at least one blood protein selected from the group consisting of factor II, factor V, factor VII, factor VIII, factor IX, factor X, factor XI, factor XII, von Willebrand factor, protein C, protein S, and protein Z. Applicant further claims the method according to claim 43, wherein the method yields a suspension that comprises at least one blood protein selected from the group consising of factor II, factor V, factor VII, factor VIII, factor IX, factor X, factor XI, factor XII, von Willebrand factor, protein C, protein S, and protein Z. Applicant further

claims the method according to claim 62, wherein the purifying yields a biological preparation that comprises at least one blood protein selected from the group consisting of factor II, factor V, factor VII, factor VIII, factor IX, factor X, factor XI, factor XII, von Willebrand factor, protein C, protein S, and protein Z. Applicant claims a biological preparation containing at least one protein having an activity, wherein the preparation is obtained by a method comprising: adsorbing a biological material to a solid carrier, wherein the biological material comprises at least one protein having an activity; incubating said biological material in the presence of an alkyl phosphate-free detergent solution, wherein the detergent solution contains at least one eluotropic salt in a total concentration of at least 200 mM, wherein during incubating the protein is desorbed into the detergent solution to yield a suspension, and contaminating microorganisms and pyrogens are inactivated; and purifying the protein from said biological preparation, wherein the biological preparation contains at least 50% of the protein activity present in the biological material. Applicant further claims the biological preparation according to claim 82, wherein the biological preparation contains at least 70% of the protein activity present in the biological material; and, wherein the biological preparation contains at least 85% of the protein activity present in the biological material.

Applicant argues that Chandra fails to teach the claimed subject matter because "the Chandra patent discloses adsorbing Factor IX to a solid phase and then treating it with just a detergent solution. Applicant further argues, "In contrast, the claimed invention, as clarified herein, incubates the biological material in the presence of the alkyl phosphate-free detergent solution that contains at least one eluotropic salt (which

can be a chaotropic agent) in a total eluotropic salt concentration of at least 200 mM (0.2M)." However, Applicant's arguments are not persuasive because Chandra teaches a method for inactivating microorganisms and pyrogens present in biological materials comprising the steps of adsorbing the biological material onto a solid phase; treating the adsorbed product with a virus or pyrogen inactivating agent; separating the solid phase and removing the residual inactivating agent; recovering the product; and purifying the product. The Chandra' method can be applied to various biomedical materials, *e.g.*, blood protein fractions and blood factors, which are adsorbed onto a solid carrier, such as an ion exchanger and resins used for affinity chromatography, *etc.* *See* Column 2, lines 22-68 to Column 3, lines 1-27. In Column 2, lines 28-68 to Column 4, lines 1-60, Chandra teaches non-ionic detergents, such as polyoxyethylene ether detergents, as inactivating agents which are present in amounts of from 0.1 to 50%, 0.5%-20%, or 1-10% based on the volume of the product. The incubation time taught by Chandra is generally in the range of 1 to 10 hours. In an attempt to provide support that Chandra fails to anticipate the instantly claimed method, Applicant points to the teachings of "Example 5", in Column 9, lines 6-24. However, Chandra clearly teaches the claimed subject matter in other examples. For example, in Column 7, line 37 to Column 8, line 56, under "Example 3", Chandra teaches a method of inactivating endotoxins (pyrogens) present in cryopoor plasma comprising adsorbing Prothrombin Complex factors including Factor IX on a DEAE-Sephadex resin, which is treated with a 2% Triton X-100 solution in 0.01 sodium citrate, 0.2 M (200 mM) sodium chloride to depyrogenate. Chandra further teaches, "Thereafter, the resin is washed three times

with aliquouts of 0.01M sodium citrate, 2M sodium chloride at pH 7.0, dialyzed and ultrafiltered against 0.13M sodium chloride at pH 7.0 to a volume of 5 ml." Chandra further teaches that the treatment results in practically no impact on Factor IX potency. In another example, *i.e.*, "Example 7", in Column 9, line 55 to Column 10, line 10, Chandra teaches the isolation of Protein C (a vitamin K-dependent protein) free of viruses by treatment with Triton X-100 at a solid phase consisting of pore glass CPG-DEAE. For instance, Chandra teaches passing cryopoor plasma spiked with VSV through a column packed with CPG-DEAE, wherein Protein C was adsorbed on the column which was treated with 2% Triton X-100 in the wash buffer, 0.01M sodium citrate, 0.2M (200 mM) sodium chloride to inactivate the virus. Chandra further teaches, "Residual Triton X-100 and other impurities are removed by washing the column extensively with buffer. Protein C is then eluted from the column by 0.25M sodium citrate, o,55M sodium chloride at pH 6.0. The eluate is dialyzed against normal physiological saline solution and a Protein C free of marker virus VSV, (less than 0.25 PFU/ml) is obtained." See entire document and claims.

The Office notes that Chandra does not expressly teach that the biological preparations prepared by his invention contain at least either 50%, 70% or 85% of the protein activity present in the biological material. However, the material to be treated, the ingredients used in the treatment thereof, and the method steps taught by Chandra are one and the same as the method instantly claimed by Applicant. Therefore, the instantly claimed beneficial effect must be inherent to the method taught by Chandra.

The Chandra' patent is deemed to anticipate the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 43-49, 51, 52, 55-62, 73, 75-79, as amended, and newly submitted Claims 82-84 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Chandra et al. (A).

Applicant's claimed invention of 43-49, 51, 52, 55-57, 62, 73, 75-79, and 82-84 was set forth above. Applicant further claims the method according to claim 43 wherein the biological material is adsorbed onto a solid carrier and said incubation is effected after the elution of the biological material from said solid carrier. Applicant further claims the method of claim 58 wherein the solid carrier is a chromatographic material. Applicant further claims the method of claim 59 wherein the chromatographic material is used in ion exchange chromatography or affinity chromatography.

The method of Chandra was set forth above. Chandra does not teach a method for microbial and pyrogen inactivation and purification of a biological matter, wherein the incubation of the eluted fraction is effected after the elution of the biological material from the solid carrier. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the referenced teaching by reversing the order of elution and incubation process steps as taught by Chandra because the order in which the process steps take place is not a critical feature of the process and will not effect the result product. Thus, the claimed invention is nothing

more than the reversed steps in the making of the preparations taught by Chandra. One of ordinary skill in the art at the time the invention was made would have been motivated to modify the Chandra' method because it would have been *prima facie* obvious to reverse the steps, as the claimed invention is nothing more than and arbitrary matter of experimental design choice in the making of a biological preparation.

According, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 43-49, 51, 52-62, 73, 75-81 as amended, and newly submitted Claims 82-90 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Chandra et al. (A) in view of Hrinda et al. (N), Eibl et al. (B, US 5,770,199) and Eibl et al. (B, 4,640,834).

Applicant's claimed invention was set forth above. Applicant further claims a method according to claim 43 wherein said elutropic salt is a chaotropic agent; and wherein said chaotropic agent is selected from the group consisting of urea, rhodanides, and guanidinium. Applicant further claims a method according to Claim 62 and Claim 76, wherein the purifying is performed by diluting the suspension and contacting the diluted suspension with a solid carrier, whereby said proteins are readsorbed to the carrier and the inactivated microorganisms and pyrogens remain with the detergent of the suspension. Applicant further claims the biological preparation according to claim 62 and 82, wherein the suspension from the incubating step is nanofiltered prior to the purifying step. Applicant further claims the biological preparation according to claim 62 and 82, wherein the suspension from the incubating step is lyophilized and then treated with heat prior to the purifying step.

The teachings of Chandra were set forth above. Chandra teaches the claimed invention except for a chaotropic agent and wherein the purifying is performed by diluting the suspension and contacting the diluted suspension with a solid carrier, whereby said proteins are readsorbed to the carrier and the inactivated microorganisms and pyrogens remain with the detergent of the suspension. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Chandra by adding a chaotropic agent and the instantly claimed process steps because Hrinda and Eibl teach chaotropic agents that are effective in inactivating microorganisms and pyrogens present in biological materials; and Hrinda teaches the instantly claimed process steps are effective in the making of purified protein products. Firstly, Hrinda teaches methods of inactivating viruses in a blood product, which comprises labile proteins and viruses, comprising contacting the blood product with chaotropic agents, e.g., sodium thiocyanate and EDTA. On page 15, lines 19-23, Hrinda further teaches that sodium thiocyanate is used in an amount of 0.5M to 2M. On page 7, lines 5-7, Hrinda teaches, "Contact of sodium thiocyanate with the blood protein-containing compositions is for about 1 to 2.5 hours, preferably at least 1 hour." The method taught by Hrinda comprises the steps of chromatographing a blood product to a carrier; eluting the chromatographed blood product; incubating the biological material to inactivate viruses; and, separating the chemical disinfectant from the active blood product by dialysis (optional step); and, physically removing the inactivated and active viruses from the blood product. *See* page 14, lines 8 to page 15, lines 1-11. Moreover, on page 17, lines 34-37, Hrinda teaches that additional purification of a protein product, *i.e.,* Factor IX, may be achieved, if desired, by readsorbing the suspension on a solid carrier. Secondly, Eibl ('199) teaches a method of inactivating infectious agents present in a biological material containing proteins

comprising contacting the biological material with chaotropic agent such as thiocyanate, urea or guanidinium salt. *See* Column 4, lines 45 to Column 5, lines 1-9. Thirdly, Eibl ('834) teaches a method of inactivating viruses in blood products, *e.g.,* coagulation factors II, VIII, XI, X, prothrombin, immunoglobulin, protein C, plasminogen, fibrinogen and fibronectin, *etc.,* by heat treatment. The method of viral inactivation via heat treatment taught by Eibl can also be used in the activation of viruses in lyophilized blood products. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the chaotropic agents taught by Hrinda and Eibl to the method taught by Chandra because Hrinda teaches that his method provides a blood product which comprises a labile blood protein free of viruses without incurring protein denaturation; Eibl ('199) teaches that treating biological materials in the presence of the disclosed chaotropic agents inactivates infectious agents while effecting a preferred biological activity of the product produced thereof; and Eibl ('834) teaches that the heat treatment of his invention is effective in destroying any reproducible filterable pathogens that might be present in a blood product. One of ordinary skill in the art would have been further motivated at the time the invention was made to add the instantly claimed ingredients and process steps to the method taught by Chandra because Hrinda teaches, "Each of these steps, i.e., pre-purification, chemical sterilization, and retentive filtration is very in reducing viral infectivity."

With regard to the claim limitations of Claims 80, 81, 85, 86, 89 and 90 wherein Applicant claims a method wherein the purifying is performed by diluting the suspension and contacting the diluted suspension with a solid carrier, whereby said proteins are readsorbed to the carrier and the inactivated microorganisms and pyrogens remain with the detergent of the suspension; wherein the suspension from the incubating step is

nanofiltered prior to the purifying step; and, wherein the suspension from the incubating step is lyophilized and then treated with heat prior to the purifying step, as each of the references of Hrinda, Eibl ('199), and Eibl ('834) teach the requisite amounts of the claimed ingredients, process steps and experimental parameters to effect the inactivation of pyrogens in a biological material by either chemical or physical means, at the time the invention was made, it would have been obvious to one of ordinary skill in the art and one would have been motivated and had a reasonable expectation of success to optimize the teachings of Chandra by adding any of the claimed process steps to provide the claimed inventions because each of the cited references teach that the process steps are effective in the making of purified, pyrogen-free blood products having desirable biological activity. Thus, the effective varying of the amounts of the ingredients, the effective varying of the experimental process steps and the effective varying of the experimental parameters used in the claimed inventions would have been no more than routine optimization and/or experimental design for one of ordinary skill in the art at the time the invention was made, given the cited references before the skilled artisan.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele C. Flood whose telephone number is (703) 308-9432. The examiner can normally be reached on 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (703) 306-3220. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Michele C. Flood

MICHELE FLOOD
PATENT EXAMINER
MCF
January 12, 2003